Cardiovascular Drugs and Therapy 19 219–226 2005

REVIEW

Can Amiodarone Prevent Sudden Cardiac Death in Patients with Hemodynamically Tolerated Sustained Ventricular Tachycardia and Coronary Artery Disease?

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Summary. **One of the most important challenges in today's cardiology is prevention of sudden cardiac death in high risk patients with coronary artery disease (CAD). Sustained hemodynamically tolerated ventricular tachycardia (HTVT) comprises up to 30% of all cases of monomorphic ventricular tachycardia in patients with CAD. While there is a consensus on treatment of hemodynamically unstable sustained ventricular tachycardia in patients with CAD, some controversies regarding the proper treatment of HTVT exist. We re-examined existing clinical evidence, controversies and current guidelines on the treatment of HTVT in patients with CAD and demonstrated that compared to implantable cardioverter-defibrillator, amiodarone is not an acceptable therapeutic option in patients with ischemic heart disease who suffer from HTVT.**

Key Words. **coronary artery disease, ventricular tachycardia, implantable defibrillators, amiodarone, sudden cardiac death, secondary prevention**

Introduction

One of the most important challenges nowadays is prevention of sudden cardiac death (SCD) in high risk patients with coronary artery disease (CAD) [1]. There is some inconsistent evidence supporting potential benefit of amiodarone in the prevention of SCD in high risk post myocardial infarction (MI) patients [2]. Development of implantable cardioverter-defibrillators (ICD) has been a dramatic advancement in the management of patients with ventricular tachycardia (VT). Several reviews have assessed the current evidence on superiority of ICD in the prevention of SCD in various patient populations with spontaneous sustained monomorphic ventricular tachycardia (MMVT) compared to amiodarone, and, based on these studies, AHA/ACC guideline has given ICD a class I indication with level of evidence: B in patients with spontaneous sustained VT (irrespective of hemodynamic status during arrhythmia) in association with structural heart disease [3,4]. While there is a consensus on treatment of hemodynamically unstable sustained VT in patients with CAD, some controversies exist regarding the proper treatment of HTVT [1,4]. This review intends to re-examine existing clinical evidence, controversies and current guidelines on the treatment of HTVT in patients with CAD.

Prevalence of MMVT and HTVT in patients with CAD and its impact on survival

Late sustained MMVT occurs in 3–5% [5] of patients after an acute MI and has been associated with a poor prognosis (relative risk of mortality: 2.6 to 9.1 according to different studies) when compared to those without a ventricular arrhythmia [6]. Several studies have assessed the effect of MMVT on survival of patients with CAD [6–10,13]. The reported annual mortality of these patients varied from 5% (in those with a left ventricular ejection fraction [LVEF] >50%) [9] to more than 40% [10] in patients with LV dysfunction. Newby et al. [7] have examined the incidence and impact of MMVT on survival of 40,895 post MI patients in the "Global Use of Streptokinase t-PA for Occluded Coronary Arteries" (GUSTO)-I trial. In GUSTO-I the incidence of late sustained MMVT was 3.5%. The overall one year mortality in 30 day survivors in the late VT group was 24.7% (mean LVEF = 46%) compared to 2.7% in patients without ventricular arrhythmias (mean LVEF = 52%). Al-Khatib et al. [11] have recently assessed the effect of late MMVT on survival of 15,042 post MI patients participating in GUSTO-III trial which confirmed the above mentioned findings of GUSTO-I trial. These results were confirmed also by a study on 26,416 patients with acute coronary syndrome [12]. The prevalence of late MMVT in these patients was 2.1% (lower than post MI patients in GUSTO-I and III), however the hazard ratio (HR) was comparable (HR = 5, 95% Confidence Interval = 3.8–6.5) to the GUSTO-I and III studies. It is worth to mention that in GUSTO I and III the mortality of patients with late

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sustained MMVT was higher compared to patients with late VF. This is in accordance to the CARE group results [14] which showed that the probability of appropriate ICD discharge is two times higher in patients with sustained MMVT compared to those with aborted SCD and VF.

A recently published guideline [1] has recommended amiodarone and beta blocker therapy as a class IIa indication and ICD, along with ablation and surgery, as class IIb recommendation for the treatment of patients with HTVT. The above mentioned statement could only be accepted if one assumes that the mortality in HTVT is significantly lower than more severely symptomatic VTs and that amiodarone therapy is equal or superior to ICD with respect to prevention of SCD in this particular group of patients.

HTVT comprises up to 30% of all cases of MMVT in patients with CAD [15,16]. Several studies have examined the effect of HTVT on survival compared to more severely symptomatic VT. Although Sarter et al. have suggested a better prognosis for HTVT [17] (however, some debates exist on their data as 64% of deaths in their study were non-sudden either due to perioperative death, recurrent infarction or progressive heart failure. Thirty seven percent of patients were treated with VT surgery with a perioperative mortality of 20%. This surgery improved the outcome in patients who survived the operation and gives an inaccurate estimate of the risk of SCD in those who survived. In addition they found that longer VT cycle length, which one could expect to be associated with more benign symptoms, is related to a higher mortality [18]). Others showed that the risk is similar to patients with more severely symptomatic VT. Raitt et al. performed a retrospective subgroup analysis of the AVID registry [15] and showed that the absence of symptoms with sustained VT does not predict a benign prognosis (see below). Olson et al. assessed the predictors of SCD in 122 patient followed for an average of 19.5 months [18] and showed that the rate of SCD is not affected by presence or absence of symptoms during MMVT.

Multiple VTs (including very rapid, poorly tolerated VTs) are commonly induced during electrophysiological (EP) testing in patients with stable VT [19]. Having these in mind, HTVT actually is a marker of substrates for re-entrant ventricular arrhythmias which may causes more malignant ventricular arrhythmias during *long term* follow up. Based on available data, ICD therapy decreases all-cause mortality in CAD patients with sustained VT, and with respect to the above mentioned findings, could also decrease the mortality in patients with HTVT. Patients with HTVT are at high risk for sudden arrhythmic death, and presumably it is not the recurrence of the stable VT that leads to SCD but a more malignant ventricular arrhythmias. Bocker et al. studied the natural course of 50 patients (82%, CAD) with HTVT who received an ICD [20]. They showed that during mean follow up of 17 months, 33 patients (66%) had 3861 episodes of ventricular tachycardia which is comparable to other studies in patients with sustained MMVT [14,21]. Ninety one percent of these episodes were terminated by antitachycardia pacing. Eleven patients (22%) had episodes of potentially life-threatening fast VT (CL <250 ms) during follow up period. In the AVID registry [18] (mean follow up of 16.9 months) the mortality rate for patients with syncopal VT was 21.2% and for asymptomatic VT was 19.7% (P = NS). Had the ICD not been implanted in the Bocker study, their patients would have had at least the same mortality as in the AVID registry. It is worth to mention that in the Bocker study (like the Electrophysiologic Study Versus Electromagnetic Monitoring trial) [22] EP studies failed to predict which patient would have more rapid VT in the follow up. In conclusion, currently available data depict that HTVT negatively affects the survival of post MI patients as more severely symptomatic VT does.

Finally, epidemiological studies have consistently shown an inverse relationship between LVEF and survival in patients with CAD [23]. When LVEF decreases below 35–40%, the risk of sudden and non-sudden cardiac death rises sharply. In patients who have an LVEF <40%, the mortality rate at 2 years after infarction is 21.5% compared with 7.6% in patients with an LVEF >40% [23–27].

A subgroup analysis of AVID showed that patients with LVEF >35% failed to benefit from ICD [28]. However, the AVID trial design had a low power to detect an ICD benefit in this small subgroup of patients during short observation period which was also terminated prematurely. These factors prevented the ICD benefit from reaching statistical significance in this small subgroup of patients. As we indicate below (see: Do we need a prospective clinical trial comparing ICDs with empiric or EP guided amiodarone therapy in CAD patients with HTVT) if we want to conduct an AVID like trial in patients with HTVT and preserved LV function one would need a sample size of 1072 patients followed for three years. Hence, had the follow up period of the AVID trial been continued in an adequate number of patients for a sufficient time period, ICD would have shown its beneficial effect in these patients (see also: Do the benefits of ICD versus Amiodarone change over time?) In addition there is another subgroup analysis of AVID which showed that in patients treated with antiarrhythmic medications (but not those treated with ICD) survival was strongly associated with LVEF. The lack of statistically significant association in ICD patients might have been related to its efficacy in terminating malignant VA *regardless* of LVEF [29].

Role of Amiodarone in the Treatment of Patients with Sustained VT

A: Empiric Amiodarone Therapy

Secondary prevention. Amiodarone suppresses premature ventricular depolarizations and episodes of

nonsustained VT, but, there have not been any placebo-controlled trials on its effectiveness on sustained VT and VF [2]. All available articles only report the outcomes of patients with aborted sudden cardiac arrest or recurrent VT treated with amiodarone alone or versus other antiarrhythmics. Some reports conclude that amiodarone is as effective, and some suggest that amiodarone is not as effective as it was shown by early promising reports. The Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation study, the only randomized clinical trial available, showed that amiodarone is superior to other conventional antiarrhythmic drugs, which we know today, increase cardiac mortality [30]. The largest follow-up of amiodarone treated patients [31] (589 patients with supraventricular tachycardia, 83% of whom had VT or VF), showed that the 5-year cumulative risk of sudden death was 22% and of total mortality, 46%. The cumulative risk of drug failure (defined as SCD, recurrence of ventricular arrhythmias, or drug withdrawal) at 5 years, was 50%. In conclusion it is difficult to reach to any definite conclusion about the efficacy of amiodarone from these uncontrolled reports.

Primary prevention. Fifteen randomized clinical trials (5864 patients), including six in post MI patients [32–37], were performed on amiodarone as a prophylaxis against SCD in moderate to high risk patients for SCD. Two meta-analyses [37,38] of these trials showed a 13 to 19% reduction in total mortality but the odds ratio was different based on the control group: the odds ratio for total mortality was lower in trials with "usual care" controls (odds ratio, 0.58; 95% CI, 0.41 to 0.83; $P = .003$) and in trials with active controls (odds ratio, 0.73; 95% CI, 0.43 to 1.25; $P = .25$) than in trials with placebo controls (odds ratio, 0.90; 95% CI, 0.76 to 1.06; $P = .20$). These two meta-analyses suggested that amiodarone therapy reduces total mortality by between 10% (placebo-controlled trials only, $P =$ NS) and 13–19% (all trials, $P = 0.03$ and $P < 0.01$ respectively) in patients with moderate to high risk of sudden cardiac death. There has been no placebo-controlled trial so far to assess amiodarone's effect in patients with HTVT.

Finally, the results of The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) confirmed the findings in the above mentioned placebo-controlled studies on amiodarone. Among patients with NYHA class II and III congestive heart failure and an LVEF $\leq$35% (23% with a history of NSVT) who were on optimal medical therapy, amiodarone (compared to placebo) did not show a beneficial effect on total mortality by intention to treat analysis (HR = 1.06, 97.5% Confidence Interval = 0.86–1.30, $P = 0.529$) [39].

B: EP-guided amiodarone therapy

Amiodarone is usually prescribed empirically (as it is recommended by ESC taskforce on SCD). Several studies have suggested that EP-guided therapy can increase the success rate of therapy with amiodarone [40–47]. In these studies lack of inducible ventricular arrhythmias after amiodarone therapy was associated with a better outcome. Lack of suppression of ventricular arrhythmias, slowing of the VT cycle length, and unchanged ventricular effective refractory period were all associated with higher long term recurrence of ventricular arrhythmias and mortality. There are three major setbacks in EP-guided amiodarone therapy. First, the success rate for complete VT suppression rate during EP studies varies between 10–40% in these studies. Second, there is no standard and widely acceptedventricular stimulation protocol for assessment of its usefulness and different protocols have been used so far. Third, amiodarone has not been tested against ICD in the above mentioned trials.

Schläpfer et al. conducted the first study aiming at a comparison between EP-guided amiodarone and ICD therapy in 84 consecutive post MI patients with sustained MMVT [16]. Aborted SCD and syncope were clinical presentations of the index arrhythmia in 40% of cases and 77% of their patients were in NYHA class = II. They showed that the outcome of the patients (including 55% with EF $\leq$35%) in their study was better with ICD than EP-guided amiodarone therapy. During follow up of 63 $\pm$ 30 months, total mortality (and SCD) was 42% (21%) in EP-guided group and 15% (2%) in ICD group. It is noteworthy that their data showed that even *complete* suppression of VT by EP-guided amiodarone therapy was not protective against risk of future SCD (Schläpfer J: Personal communication).

C: adjunctive amiodarone in patients with ICD

No empiric antiarrhythmic therapy (including amiodarone) is currently indicated in patients who received an ICD. Up to 40% of patients receiving an ICD develop "electrical storm," defined as two or more episodes of VT and/or VF in a one day period [48,49]. These patients frequently receive multiple ICD shocks, which severely impair quality of life. Intravenous followed by oral amiodarone results in successful management and possibly a long-term effect similar to patients who do not have electrical storm [48,49].

The OPTIC (Optimal Pharmacological Therapy in Implantable Cardioverter) study currently assesses the potential benefit of antiarrhythmic medications in reduction of ICD therapy and electrical storm. In OPTIC the patients are randomize to β-blocker, amiodarone plus β-blocker, or sotalol. A sub-study of the OPTIC study will also assess defibrillation threshold before and after drug therapy in patients randomized to the above mentioned drugs [48]. Amiodarone may have some other potential benefits in patients with ICDs including the prevention of supraventricular tachyarrhythmias, which could cause inappropriate ICD discharges; and the prevention of nonsustained but

symptomatic ventricular arrhythmias. Further studies are warranted to clarify this issue [50].

D: role of amiodarone in hybrid therapy of HTVT

Although several studies have established the role of catheter ablation of VT (including HTVT) as an adjunctive therapy to ICD in patients with CAD who receive frequent high voltage therapies [51–54], few have evaluated the role of catheter ablation plus adjunctive amiodarone in patients with HTVT [55].

Della Bella et al. in a non-randomized prospective study (median follow up of 41.5 months), evaluated the outcome of catheter ablation and adjunctive amiodarone and/or beta-blocker therapy in 124 (mean age 64 ± 9 years, with EF >30% in 2/3 of cases) post-MI patients with HTVT (24 of whom had an ICD). The procedure of catheter ablation was successful (defined as termination and prevention of induction of all clinical and inducible VTs) in 73% of patients and after ablation 86% of patients received amiodarone and/or a beta blocker as an adjunctive therapy. The rate of all cause mortality and sudden cardiac death during the study period were 12 and 2.6%, respectively [55]. However, several points merit consideration. Although the mortality was relatively low during follow up, the rate of recurrent VT remained high even among patients with an initially successful procedure. Among these patients the 1 and 3 year VT recurrence rates were 19 and 27%, respectively. In addition, as this study was non-randomized we cannot conclude that this combination therapy is as effective as or superior to ICD in patients with HTVT [55].

In conclusion, based on currently available data [18,20,52] catheter ablation (with or without adjunctive antiarrhythmic therapy) can not be recommended as an alternative to ICD in patients with HTVT. However, in case of frequent ICD shocks, amiodarone and/or catheter ablation should be considered as an adjunctive treatment.

Do the benefits of ICD versus amiodarone change over time?

A meta-analysis of the CASH, CIDS and AVID trials showed a significant reduction in death from any cause with ICD, hazard ratio (ICD:amiodarone) of 0.72 (95% CI, 0.60 to 0.87; P: 0.0006) [56]. However, neither the CIDS nor the CASH trials alone demonstrated a significant benefit of the ICD over amiodarone. Bokhari et al. [57] have recently published the 11 year follow up in a subset of patients of CIDS trial. After a mean follow-up of 5.6 ± 2.6 years in 120 patients, there were 28 deaths (47%) in the amiodarone group, compared with 16 deaths (27%) in the ICD group ($P = 0.0213$). Total mortality was 5.5% per year in the amiodarone group versus 2.8% per year in the ICD group (hazard ratio of amiodarone: ICD, 2.011; 95% confidence interval, 1.087 to 3.721; $P = 0.0261$). In the amiodarone group, 49 patients (82% of all patients) had side effects related to amiodarone, of which 30 patients (50% of all patients) required discontinuation or dose reduction; 19 patients crossed over to ICD because of amiodarone failure ($n = 7$) or side effects ($n = 12$) [57]. The authors showed that during long term follow up the benefit of the ICD over amiodarone increases and most amiodarone-treated patients eventually develop side effects, have arrhythmia recurrences, or die. This finding has been confirmed recently by Salukhe et al. [58]. They estimated, from published data of 8 major ICD trials, the cumulative benefit life-years gained and calculated the dependency of the benefit on duration of follow-up. They found that the number of life-years gained from one device implantation increases with length of follow-up. Importantly, this increase is markedly *nonlinear*. Within a 3-year span, the benefit rises with the square of time (gain $\alpha\ t^{1.94}$, $R2 = 0.998$, $P = 0.001$). They concluded that the expected benefit in life span (life-years gained) for a patient who has an ICD is dramatically dependent on the time window over which the benefit is assessed. It is important to consider the effect of follow-up duration while interpreting the results and outcome in ICD trials [58].

Concerns have recently been raised about the role of ICD therapy in apparently stable patients with left ventricular dysfunction several years after MI [59]. It is widely believed that among patients with CAD as the time passes from MI the risk of SCD, and hence, the potential benefit of ICD over amiodarone is diminishing. Long-term follow-up of MI survivors conducted in the 1970s and 1980s indicated that the greatest risk of sudden death was in the initial 6 to 12 months after infarction, particularly in high-risk subgroups such as those with impaired ventricular function [60–62].

Wilber and his colleagues analyzed the time dependence of mortality risk after MI in the MADIT II cohort and evaluated whether long-term survival benefit diminished as a function of elapsed time from infarction to ICD implantation [63]. They found that in contrast to early reports, mortality risk in the MADIT II cohort did not diminish as a function of time from MI; instead, it actually increased. In addition, the survival benefit associated with ICDs appears to be greater for remote MI and remains substantial for up to ≥15 years after MI. They also found a trend toward increasing device benefit with remote MI although this did not reach statistical significance [63]. In conclusion the above mentioned studies have shown that the benefit of ICD over amiodarone increases over time (Fig. 1). This effect is observed in both primary and secondary prevention trials.

Do we need a prospective clinical trial comparing ICDs with empiric or EP guided amiodarone therapy in CAD patients with HTVT?

Although there has been no clinical trial (as a gold standard in medical practice) specifically conducted in

patients with HTVT, all the above mentioned data suggest that CAD patients presenting with HTVT have at least as high a total mortality rate as patients presenting with more severely symptomatic VT, and that amiodarone (empiric or EP guided) is not an appropriate option for treatment of patients with sustained MMVT, and an ICD is the treatment of choice similar to patients with unstable VT.

It is sometimes not possible and/or practical to perform a randomized controlled study in every subset of patients at risk [64]. When we have enough reliable data to calculate the risk of adverse event of interest in patients at risk, and a reliable assessment of the beneficial effect of intervention, risk modelling may be used as an alternative [64]. Exner and Klein have suggested that based on available data we can extrapolate the results of available trials with ICD and there is no need to perform a clinical trial in all subsets of patients at high risk for SCD [64]. They estimated that at the completion of the follow up period of SCD-HeFT the ICD would show a statistically significant absolute risk reduction in total mortality (compared to placebo) of 7.3–8.6%, which is confirmed by results of SCD-HeFT [39]. At the completion of the follow up period, ICD resulted in nearly 8% absolute risk reduction in total mortality compared to placebo.

Suppose that we want to assess the effect of ICD vs. amiodarone on total mortality (as primary end point) in patients with HTVT with a clinical trial having a 3 year follow up (Inclusion is 2 years +2 years follow up period after inclusion) and a power of 95% with no interim analysis. We estimate that the total mortality rate would be around 9%/year in the amiodarone group and ICD would reduce the total annual mortality by 50% (the mode of death in patients with HTVT is arrhythmic in at least 61% of cases [63–67] and ICD will effectively terminate these arrhythmias in more than 90% of cases [68], so one can expect that ICD would reduce the total annual mortality by at least 50%.) compared to the control group. Based on these assumptions and for a 5% significance level, 2-sided log-rank test of equality of survival curves, 89 events are required during the follow up period which corresponds to a sample size of 536 patients randomized to ICD or amiodarone (Fig. 1). If we want to conduct such a trial only in those patients who have preserved LV function with an estimated annual mortality of ≈5%, the calculated number will be nearly double. We however believe that this trial is not necessary as the bulk of evidence (see above) supports the superiority of ICD in patients who suffer from HTVT, and there would be serious ethical consideration in conducting such a clinical trial.

Conclusion

Despite current controversies and differences, the available data show that CAD patients with HTVT have a similar prognosis as more severely symptomatic VT and therefore amiodarone is not an acceptable treatment in the ICD era in these patients. ICD is the preferred mode of therapy in this setting.

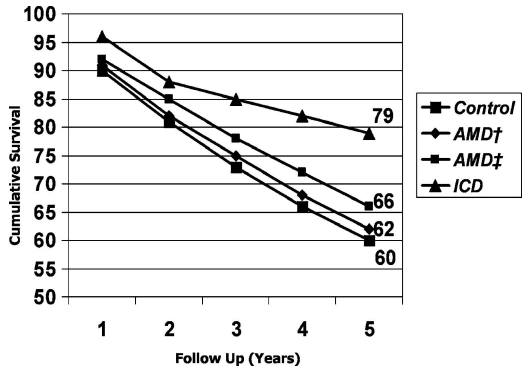

Fig. 1. *Survival curves¶ during hypothetical 5 year follow up of in a low risk group of patients (e.g. those with preserved LV function) treated with ICD vs. amiodarone and control group*. (*The annual all cause mortality assumed to be 9% in AMD group and ICD expected to decrease all-cause mortality by 50%. If we randomize 536 patients equally to ICD and AMD group, at the end of three year follow up 89 events would happen and the difference would reach to statistical significance by a 95% power. †The calculated survival is based on 10% reduction in all-cause mortality by AMD. ‡The calculated survival is based on 20% reduction in all-cause mortality by AMD,¶ Note that survival curves diverge dramatically after second year of follow up and reach to a statistically significant difference after three years of follow up (see above). Had the follow up been stopped after a two years period (like AVID), the difference in mortality would have not reached to statistical significance. This example signifies the effect of follow up duration on assessment of treatment outcome in ICD trials (see also: Does the ICD Benefit Change over Time?)) AMD: Amiodarone.*

Acknowledgment

The authors would like to thank Elham Hasheminejad, M.D. and Babak Kazemi, M.D. for reviewing of the manuscript. The authors would also like to thank kristof DAEMS for the sample size calculations used in this article.

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